UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,177	12/31/2003	Andrew P. Levy	P-7339-US	7660

49443 7590 07/02/2008

Pearl Cohen Zedek Latzer, LLP
1500 Broadway
12th Floor
New York, NY 10036

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
07/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,177	LEVY, ANDREW P.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,12-15 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12-15 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed November 26, 2007 and April 14, 2008. Currently, claims 1, 12-15, 26-28 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 12-15, 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

4. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method of determining a potential of a diabetic patient to benefit from vitamin E therapy for treatment of a cardiovascular complication comprising cardiovascular death or myocardial infarction by determining a haplotype phenotype of the diabetic patient and thereby determining the potential of the diabetic patient to benefit from said vitamin E therapy.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the art

The art teaches the effect of vitamin therapy on the progression of coronary artery atherosclerosis varies by haptoglobin type in postmenopausal women (Levy et al. Diabetes Care, Vol. 27, No. 4, pages 925-930, April 2004). Levy teaches that changes in the MLD as a function of haptoglobin phenotype and vitamin therapy were analyzed. The analysis of changes in LDL and HDL levels with and without vitamin therapy were analyzed in diabetic patients. The LDL levels in Diabetic patients was not significantly different between vitamin and placebo treated (see Table 4). Levy asserts that the benefit of antioxidant therapy with vitamin CX and E on progressive coronary artery stenosis may be restricted to woman with the Hp 1-1 phenotype 9page 927, col. 3).

Levy (Diabetes Care, Vol. 27, No. 11, pages 2767, November 2004) teaches "the absence of any statistical interaction indicates that these data do not support the hypothesis that the effects of vitamin E differed by Hp phenotype. Therefore, the results

noted above in Hp 2-2 diabetic individuals demonstrating a significant reduction in CV death and myocardial infarction could be spurious and clearly require prospective testing in future trials." Thus Levy teaches the HOPE study cannot be relied upon, but rather replication is advised.

Levy (Pharmacology & Therapeutics, Vol. 112, pages 501-512, 2006) teaches atherosclerotic cardiovascular disease (CVD) was studied in determining whether antioxidant vitamin therapy may or may not be beneficial for a given patient with diabetes. Levy teaches there are a variety of antoxidants (vitamin E, vitamin C, folate, beta carotene, selenium, Q-10). Levy teaches vitamin E reduced CVD death and myocardial infarction in Hp 2-2 DM individuals in the HOPE study. However, no benefit was found from vitamin E supplementation in the diabetic cohort alone (page 510, col. 2). Levy teaches that there was no benefit observed in Hp 1-1 or Hp 2-1 individual with DM. Further, the WAVE and HPS studies did not find any benefit associated with antioxidant vitamin in the Hp 2 DM population. Levy suggests a 4-year double blinded clinical trial with 1500 Hp 2-2 DM individuals is being conducted in order to try to validate the findings presented above for Hp 2-2 DM individuals. Thus, it is clear that a single study show narrow results, but the results were not replicated in two additional studies.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such

irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Guidance in the Specification and Working Examples

The specification has analyzed vitamin E and Ramipril which are deemed to be two particular anti-oxidant therapies. The specification teaches there is a 100% concordance between the haptoglobin phenotype as determined from plasma and the haptoglobin genotype as determined from genomic DNA by the PCR. As seen in Table 5 of the instant specification (page 45), the analysis based on DM patients only demonstrated a statistically significant result for Hp 2-2 phenotype in CV death and MI when treated with vitamin E.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied.

The study, as reviewed by Levy (2006) appears to be only one of 3 studies that was performed. No replication of the data was obtained in the additional studies in the WAVE or and HPS studies. The WAVE and HPS studies did not find any benefit associated with antioxidant vitamin in the Hp 2 DM population. In fact Levy suggests a 4-year double blinded clinical trial with 1500 Hp 2-2 DM individuals is being conducted in order to try to validate the findings presented above for Hp 2-2 DM individuals. Furthermore, Levy (Diabetes Care, Vol. 27, No. 11, pages 2767, November 2004) teaches "the absence of any statistical interaction indicates that these data do not support the hypothesis that the effects of vitamin E differed by Hp phenotype. Therefore, the results noted above in Hp 2-2 diabetic individuals demonstrating a significant reduction in CV death and myocardial infarction could be spurious and clearly require prospective testing in future trials." Thus, the art clearly teaches the need for replication and reliability.

This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the specification and the art do not provide a reliable association between anti oxidant therapies and benefits to cardiovascular complications in diabetic patients. Further, the prior art and the specification provides insufficient guidance to overcome the art

recognized problems for association studies. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that the amendments to the claims overcome the rejection. The response asserts that the correlation is provided in Table 5 of the specification. This argument has been considered but is not convincing. The post filing date art illustrates the results provided in Table 5 were unable to be replicated. Levy (Diabetes Care, 2004) specifically states "the absence of any statistical interaction indicates that these data do not support the hypothesis that the effects of vitamin E differed by Hp phenotype. Therefore, the results noted above in Hp 2-2 diabetic individuals demonstrating a significant reduction in CV death and myocardial infarction could be spurious and clearly require prospective testing in future trials." Thus Levy teaches the HOPE study cannot be relied upon, but rather replication is advised.

Moreover, Levy (Pharmacology & Therapeutics, 2006) specifically teaches the WAVE and HPS studies did not find any benefit associated with antioxidant vitamin in the Hp 2 DM population. Levy suggests a 4-year double blinded clinical trial with 1500 Hp 2-2 DM individuals is being conducted in order to try to validate the findings

presented above for Hp 2-2 DM individuals. Thus, it is clear that a single study shows narrow results, but the results were not replicated in two additional studies. Therefore, it is unpredictable whether the skilled artisan could accurately predict whether a diabetic patient could benefit from vitamin E therapy for treatment of cardiovascular death or MI without further experimentation to confirm the single study. Two further, large studies were unable to confirm the results.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

5. No claims allowable.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine A Goldberg/
Primary Examiner, Art Unit 1634

July 2, 2008